UNITED STATES COURT OF APPEALS
FOURTH CIRCUIT

No. 02-1351

Argued: January 22, 2003
Decided: July 16, 2003

UNITED STATES OF AMERICA,

Plaintiff-Appellant,

—v.—

ST. LOUIS UNIVERSITY, a corporation,

Defendant-Appellee.

ARGUED: Mary McElroy Leach, Senior Trial, United States Department Of Justice, Washington, D.C., *for Appellant*. Marc Simon Moller, Kreindler & Kreindler, New York, New York, *for Appellee*. ON BRIEF: Robert D. McCallum, Jr., Assistant Attorney General, Thomas M. DiBiagio, United States Attorney, Jeffrey Axelrad, Director, Torts Branch, Civil Division, United States Department Of Justice, Washington, D.C.; Daniel E. Troy, Chief, Eric M. Blumberg, Deputy Chief for Litigation, Michael N. Druckman, Associate Chief for Biologics, U.S. Food & Drug Administration, Rockville, Maryland; Alex M. Azar, II, General, Department Of

Health And Human Services, Washington, D.C., *for Appellant*. Mark R. Dunn, Herzog, Crebs & McGhee, L.L.P., St. Louis, Missouri; Stanley P. Kops, Bala Cynwyd, Pennsylvania; Rex Carr, Carr, Korein, Tillery, Kunin, Montroy & Glass, East St. Louis, Missouri, *for Appellee*.

Before NIEMEYER, LUTTIG, and TRAXLER, *Circuit Judges*.

Reversed and remanded by published opinion. Judge TRAXLER wrote the majority opinion, in which Judge NIEMEYER joined. Judge LUTTIG wrote a dissenting opinion.

OPINION

TRAXLER, *Circuit Judge*:

St. Louis University ("SLU") paid a $16 million Missouri state-court judgment to the family of a boy who became paralyzed after receiving Orimune, an oral polio vaccine. SLU sought contribution from American Cyanamid, the parent company of the vaccine manufacturer, and United States government, which tested and approved the vaccine. The district court granted summary judgment in favor of Cyanamid and the government, concluding that SLU's contribution claims were barred by principles of collateral estoppel. We reversed

and remanded. *See St. Louis Univ. v. United States*, 5 Fed.Appx. 133 (4th Cir. 2001); *American Cyanamid v. St. Louis Univ.*, 5 Fed.Appx. 131 (4th Cir. 2001). After remand, on motions and cross-motions for summary judgment, the district court concluded that the government, but not Cyanamid, was liable in contribution to SLU. The government appeals the district court's conclusion that it can be required to contribute to the state-court judgment entered against SLU.[1] We reverse and remand.

I. BACKGROUND

A. The Vaccine

There are three types of poliomyelitis; "Type I can be contracted only from a Type I virus, Type II only from a Type II virus and Type III only from a Type III virus." *In re Sabin Oral Polio Vaccine Prods. Liab. Litig.*, 743 F.Supp. 410, 412 (D.Md.1990). In the 1950s, an oral polio vaccine ("OPV") was developed that used a live but attenuated or weakened polio virus. "Like all vaccines cultivated from live viruses, OPV creates immunity by inducing a mild infection in the recipient." *Stuart v. American Cyanamid Co.*, 158 F.3d 622, 625 (2d Cir.1998). However, OPV also carries with it a risk that a recipient (or someone in close contact with the recipient) will contract the disease through the vaccine.

OPV is produced by passing wild virus of each type through an animal host to develop a "strain" of attenuated virus. The vaccine manufacturer uses the strain to

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[1] In *American Cyanamid Co. v. St. Louis University*, 336 F.3d 307, 2003 WL 21660347 (4th Cir. 2003), SLU appeals the district court's rejection of its contribution claim asserted against Cyanamid. We address that appeal in a separate opinion.

grow a "seed" of each type of virus, the seeds are used to produce monopools of each type of virus, and "lots" of that virus type are derived from the monopools. Lots from each type of virus are then combined into a single "trivalent" pool, from which a trivalent vaccine can be produced to protect against all three types of polio. *See Berkovitz v. United States,* 486 U.S. 531, 541, 108 S.Ct. 1954, 100 L.Ed.2d 531 (1988).

The United States government approved OPV in 1960 and in 1961 adopted regulations governing the manufacture of the vaccine. The regulations required OPV to satisfy certain "neurovirulence" tests.

> Neurovirulence is the capacity of an infectious agent to produce pathologic effects on the central nervous system. In this context, it refers to the vaccine's ability to cause paralytic poliomyelitis. The neurovirulence of a vaccine product is tested by injecting the product into monkeys. The product meets the neurovirulence criterion only if a specified number of the animals survive and a comparative analysis demonstrates that the neurovirulence of the vaccine product does not exceed the neurovirulence of a reference product previously selected by the agency.

Berkovitz, 486 U.S. at 545 n. 9, 108 S.Ct. 1954 (internal quotation marks omitted). Under the original OPV regulations, a given monopool could be used to produce vaccine only if its neurovirulence did not exceed that of the reference vaccine and the monopool was one of five consecutively made monopools that all satisfied the monkey neurovirulence test.

The government substantially amended the monkey neurovirulence regulations in 1991, in part because studies did not show a correlation between higher neurovir-

ulence scores in monkeys and the incidence of vaccine-associated polio in humans. *See Additional Standards for Viral Vaccines,* 56 Fed.Reg. 21418, 21420 (May 8, 1991) ("No single vaccine lot has been associated with an increased incidence of poliomyelitis. The lots that have been identified as associated with a case of paralytic poliomyelitis have had typically low scores when tested by FDA and the manufacturer for neurovirulence in monkeys."). In 1996, the FDA repealed a number of regulations, including the oral polio vaccine regulations. *See Revocation of Certain Regulations,* 61 Fed.Reg. 40153, 40155 (August 1, 1996).

B. The State Court Action

The state-court judgment paid by SLU arose from SLU's actions in treating 3-month old Danny Callahan. Approximately one month after receiving a dose of Orimune, Danny developed a fever and a perirectal abscess. He was treated at Cardinal Glennon Hospital by hospital and SLU employees. Although the abscess improved, Danny's legs and left arm were permanently paralyzed. Type III polio virus was isolated in Danny's stool, and doctors ultimately concluded that Danny suffered from vaccine-associated polio.

The plaintiffs' theory of the case was that SLU improperly treated Danny's abscess by giving him the wrong kind of antibiotic. The improper treatment allowed the release of endotoxins, which suppressed Danny's immune system during a time when the polio virus from the vaccine was still replicating in Danny's gastrointestinal tract. Because Danny's immune system was compromised, the attenuated polio virus in the vaccine was able to replicate fast enough to overcome his suppressed immune system, resulting in poliomyelitis.

The plaintiffs' experts testified that if the abscess had immediately been incised and drained as required by the standard of care, and if Danny had been treated with an appropriate antibiotic, the endotoxins would not have been released and his immune system would not have been suppressed. Thus, the expert witnesses testified that if Danny had been treated properly, he would not have been paralyzed by the polio vaccine. The jury's $16 million verdict in favor of the plaintiffs was affirmed by the Missouri Supreme Court. *See Callahan v. Cardinal Glennon Hosp.*, 863 S.W.2d 852 (1993) (en banc).

C. *In re Sabin*

While *Callahan v. Cardinal Glennon Hospital* was proceeding through the Missouri state courts, multi-district Orimune cases filed against the United States government under the Federal Tort Claims Act were transferred to the District of Maryland for resolution of the common legal and factual questions. *See In re Sabin Oral Polio Vaccine Prods. Liab. Litig.*, 743 F.Supp. 410 (D.Md.1990); *In re Sabin Oral Polio Vaccine Prods. Liab. Litig.*, 763 F.Supp. 811 (D.Md.1991); *In re Sabin Oral Polio Vaccine Prods. Liab. Litig.*, 774 F.Supp. 952 (D.Md.1991) ("*Sabin III*").[2] The *Sabin* plaintiffs contracted polio after receiving the Orimune vaccine or after coming into contact with a recipient of the vaccine. They sued the government, alleging, *inter alia,* that the government negligently approved for release the vaccine lots which contained the doses given to the plaintiffs, even though the vaccine seeds from which the lots were derived did not meet the neurovirulence standards set forth in the governing regulations.

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[2] The district judge presiding over the cases currently before us also presided over the *In re Sabin* cases.

The district court ultimately concluded that the government could be held liable for approving vaccine lots that did not comply with the regulatory requirements for neurovirulence. Applying the "Good Samaritan" principles of the *Restatement (Second) of Torts,* the district court determined that the government, by violating its own regulatory standards and approving for release vaccine derived from seeds that exceeded the neurovirulence standards, had increased the risk of harm for those receiving the vaccine, which proximately caused the plaintiffs' injuries. *Sabin III,* 774 F.Supp. at 958. This court affirmed the district court's causation and liability determination. See *In re Sabin Oral Polio Vaccine Prods. Liab. Litig.,* 984 F.2d 124 (4th Cir.1993) (per curiam) ("*Sabin IV*"). The Orimune vaccine received by Danny Callahan was derived from one of the vaccine seeds that the district court in the *Sabin* cases concluded were improperly approved by the government.

II. THE CONTRIBUTION ACTION

After the Missouri Supreme Court affirmed the *Callahan* verdict, SLU filed a contribution action in Maryland against the United States, alleging that Danny Callahan's polio was caused by the governmental failings identified in the *Sabin* cases. The government moved for partial summary judgment, arguing that SLU was barred by collateral estoppel from relitigating the *Callahan* jury's conclusion that SLU's malpractice caused Danny's polio. The district court agreed, concluding that SLU was prohibited from relitigating the facts that the court believed the *Callahan* jury necessarily found in order to reach its verdict against SLU: (1) that SLU breached the applicable standard of care when treating Danny's abscess; (2) that Danny's immune system would not have been

suppressed but for SLU's inadequate treatment of the abscess; (3) that, but for the suppressed state of Danny's immune system, the live polio virus contained in the vaccine would not have been able to replicate fast enough to cause polio; and (4) that, but for SLU's negligence, Danny would not be paralyzed. The district court's collateral estoppel order prevented SLU from arguing that it was not negligent at all or that any negligence on its part did not contribute to Danny's polio, but the ruling allowed SLU to proceed on any theory consistent with the *Callahan* verdict. Thus, after the collateral estoppel order, SLU could still prevail if it could establish that an immunosuppressed child would not have contracted polio from a vaccine that complied with all regulatory requirements.

After the collateral estoppel ruling, the parties engaged in eighteen months of discovery. The government then moved for summary judgment on the ground that SLU could not prove that the government's negligence caused Danny's polio. The district court reviewed the evidence submitted by SLU and concluded that it was insufficient, given the *Callahan* findings, to establish a causal connection between the government's negligence and Danny's injuries. The district court therefore granted summary judgment to the government on SLU's contribution claim.

We reversed and remanded, concluding that the district court improperly applied Missouri law when it held that the *Callahan* jury verdict had collateral estoppel effect on SLU's contribution action against the government. We explained that Missouri law did not limit SLU to causation theories predicated on the *Callahan* jury's implicit conclusion that Danny would not have contracted polio but for SLU's negligence which resulted in the suppression of his immune system. However, the dis-

trict court had limited SLU during discovery to causation theories consistent with its ruling as to the collateral estoppel effect of the *Callahan* judgment, and the district court premised its order granting summary judgment on SLU's failure to present evidence of causation consistent with its collateral estoppel ruling. Because of the district court's error with regard to the collateral estoppel issue, we reversed the district court's grant of summary judgment to allow SLU an opportunity to develop other appropriate theories of causation.

After remand, SLU offered no new evidence, deposed no new witnesses, and offered no new theory of causation. Instead, it relied almost exclusively on the fact that in the *Sabin* cases, the court determined that the government's regulatory violations caused the injuries at issue. SLU argued that Danny Callahan's polio vaccine came from one of the seeds that the district court in *Sabin* had concluded the government negligently approved in violation of its own regulatory standards. Since the *Sabin* court had concluded that the government's failings proximately caused the injuries of the *Sabin* plaintiffs, SLU suggested that those same regulatory violations must also be held to have proximately caused Danny's injuries.

The district court agreed with SLU. Applying the same analysis the court had used in *Sabin III,* the district court concluded that the government's negligence in approving vaccine that did not satisfy the neurovirulence standards caused Danny's polio. The district court therefore granted partial summary judgment to SLU, concluding that the government was liable in contribution to SLU, but reserving for later the determination of the extent of the government's liability to SLU.[3]

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[3] The district court certified the order as appropriate for immediate review, and this court granted the government permission to bring this interlocutory appeal. *See* 28 U.S.C.A. § 1292(b) (West 1993).

III. ANALYSIS

The government's liability in contribution, of course, is dependent on SLU's ability to establish that the government can be held liable on the tort claim in the underlying action. *See United States v. Yellow Cab Co.*, 340 U.S. 543, 546-50, 71 S.Ct. 399, 95 L.Ed. 523 (1951) (concluding that the waiver of sovereign immunity under the Federal Tort Claims Act encompasses claims for contribution if the law of the relevant state would hold a private individual liable for contribution in the same circumstances); *Gramex Corp. v. Green Supply, Inc.*, 89 S.W.3d 432, 442 (Mo.2002) (en banc) ("To maintain an action for contribution, both the party seeking contribution and the defendant against whom contribution is sought must be tortfeasors, originally liable to the plaintiff-injured party." (alterations and internal quotation marks omitted)). The government contends that SLU presented no evidence showing that the government's violations of the original polio vaccine regulations proximately caused the injuries suffered by Danny Callahan. According to the government, the district court's approach to the case amounts to the imposition of absolute liability for the government, which is inconsistent with the requirements of the Federal Tort Claims Act and does not meet the causation requirements of Missouri law. Given the absence of any admissible proximate cause evidence, the government contends that the district court must have reached its decision by giving collateral estoppel effect to its decision in *Sabin III*, but that collateral estoppel cannot be applied against the government in this case.

A.

We first consider the government's arguments as to whether the decisions in the *Sabin* cases must be given controlling effect in this litigation. At the outset, we can dispense with the government's claim that the district court improperly gave collateral estoppel effect to the *Sabin* decisions, an action which might well have been error. *See United States v. Mendoza,* 464 U.S. 154, 162, 104 S.Ct. 568, 78 L.Ed.2d 379 (1984) (rejecting the use of offensive nonmutual collateral estoppel against the government). The district court expressly did not give the *Sabin* cases collateral estoppel effect. Instead, it appears that the court viewed the cases as establishing binding precedent on the question of proximate cause. *See St. Louis Univ. v. United States,* 182 F.Supp.2d 494, 500 n. 5 (D.Md.2002) ("I am not relying upon the doctrine of collateral estoppel, which may not be invocable against the government. I am simply following my reasoning in *Sabin III* that was affirmed on appeal." (citation omitted)). The question, then, is whether *Sabin III* and our decision in *Sabin IV* serve as binding precedent in this case. We think the answer to that question is no.

Under the Federal Tort Claims Act, state law, not federal law, serves as "the source of substantive liability." *FDIC v. Meyer,* 510 U.S. 471, 478, 114 S.Ct. 996, 127 L.Ed.2d 308 (1994). The Act requires the government's liability to be determined "in accordance with the law of the place where the act or omission occurred." 28 U.S.C.A. § 1346(b)(1) (West Supp.2003). The Supreme Court has concluded that the "law of the place" refers to the "whole law," including choice-of-law principles of the state where the negligent act or omission occurred. *See Richards v. United States,* 369 U.S. 1, 11, 82 S.Ct. 585, 7 L.Ed.2d 492 (1962).

Because the government's actions with regard to the polio vaccine took place in Maryland, *see Sabin III*, 774 F.Supp. at 953-54, Maryland law, including its choice-of-law principles, governs this case, just as it governed the *Sabin* cases. Under Maryland's choice-of-law principles, the law to be applied in tort cases is the law of the state where the injury was suffered, not where the negligent act occurred. *See Johnson v. Oroweat Foods Co.*, 785 F.2d 503, 511 (4th Cir.1986). Danny Callahan was injured in Missouri, so Missouri law applies to SLU's claim against the government. But the plaintiffs in the *Sabin* cases were residents of Maryland and Florida and suffered their injuries in those states. Thus, the proximate cause determination in *Sabin III* was reached by applying Maryland and Florida law, while the proximate cause determination in this case must be made by applying Missouri law. Accordingly, notwithstanding the factual overlap of the cases, the analyses of *Sabin III* and *Sabin IV* simply do not govern this case.[4]

B.

Under Missouri law, a plaintiff seeking to hold a defendant liable in tort must establish the existence of a duty on the part of the defendant to protect the plaintiff, a breach of that duty, and damages caused by the breach. *See, e.g., L.A.C. ex rel. D.C. v. Ward Parkway Shopping Ctr. Co.*, 75 S.W.3d 247, 257 (Mo.2002) (en banc). In this case (and the *Sabin* cases), the district court con-

[4] Even assuming that SLU is correct in its contention that the tort laws of Maryland and Missouri are similar, it makes little sense for this court to apply Missouri law by way of *Sabin III* and *Sabin IV*, cases that applied Maryland and Florida law. Instead, we will go directly to the source and consult Missouri cases to determine whether SLU has satisfied the requirements of Missouri law.

cluded that the government's duty arose under the "Good Samaritan" doctrine, through which liability may be imposed for the negligent execution of voluntarily undertaken duties. *See Hoover's Dairy, Inc. v. Mid-America Dairymen,* 700 S.W.2d 426, 432-33 (Mo.1985) (en banc) (following Good Samaritan standards set forth in *Restatement (Second) of Torts* §§ 323, 324A (1965)). For purposes of this litigation, the government has agreed to be bound by the findings in the *Sabin* cases that it breached its duty by violating the OPV regulations. *See St. Louis Univ.,* 182 F.Supp.2d at 498. Thus, the only issue before the district court was whether SLU could establish that Danny Callahan's injuries were caused by the government's breach of duty.

The district court concluded that SLU had sufficiently established that the government's regulatory violations caused Callahan's injuries. The court explained that in *Sabin III,*

> I held that proximate cause was established by the mere fact that if seeds 45 B 85 and 45 B 165 had not been in use, the vaccine giving rise to the injuries would not have been manufactured. The evidence clearly establishes that but for the United States's negligence, the seeds would not have been used. I went on to reject an ancillary contention made by the government that proximate cause was dispelled by the fact that the specific lots involved in the two cases under consideration had met the regulatory neurovirulence criteria, and I concluded that the causal connection between the regulatory violations and plaintiffs' injuries are logical, sensible and direct. The Fourth Circuit affirmed this holding on appeal.
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> My reasoning in *Sabin III* is equally applicable here. This can be most easily seen by hypothesizing

> that SLU is correct in contending that the immunosuppression allegedly caused by its malpractice played absolutely no role in making Callahan susceptible to contracting polio from OPV. If that is true, Callahan stands in exactly the same position as did the plaintiffs in other *Sabin* cases because in that event the sole cause of his polio was the vaccine. Likewise, even if the immunosuppression did play some role in the disease process, Callahan's exposure to the oral vaccine had to be a contributing cause to his paralysis. The isolation of Type III polio virus in Callahan's stool demonstrates he contracted polio, and no one suggests that the immunosuppression alone could have caused the disease. Accordingly, as I held in *Sabin III*, Callahan was exposed to the virus as a consequence of the government's violation of the OPV regulations. If the government had not wrongfully approved the seed from which the vaccine was derived, Callahan would never have been administered a dose of Orimune and would never have contracted polio even if he had been immunosuppressed. This "but for" relationship meets the standard of proximate cause under Missouri law just as it does under the law of Maryland and Florida applicable in *Sabin III*.

St. Louis Univ., 182 F.Supp.2d at 499-500 (footnotes, alterations, and internal quotation marks omitted).

We assume, of course, that *Sabin III* and *Sabin IV* properly applied Maryland and Florida law.[5] Nonethe-

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[5] The government points out that when this court in *Sabin IV* affirmed the proximate cause analysis in *Sabin III*, we relied on *Waffen v. United States Department of Health & Human Services*, 799 F.2d 911 (4th Cir.1986), which considered causation requirements under Maryland law in the context of a claim for loss of chance of survival. Subsequent cases from this court and Maryland state courts

less, it is clear that the approach taken in the *Sabin* cases is inconsistent with the requirements of Missouri law, which governs this case. Under Missouri law, a plaintiff must establish both causation-in-fact and proximate cause. *See Callahan*, 863 S.W.2d at 862, 865; *Robinson v. Missouri State Highway & Transp. Com'n*, 24 S.W.3d 67, 77 (Mo.Ct.App.2000) (per curiam).

> A defendant's conduct is the cause in fact of a plaintiff's injuries where the injuries would not have occurred but for that conduct. Proximate cause is not causation in fact, but is a limitation the law imposes upon the right to recover for the consequences of a negligent act. The requirement of proving proximate cause absolves those actors whom it would be unfair to punish because of the attenuated relation which their conduct bears to the plaintiff's injury.

Robinson, 24 S.W.3d at 77 (citations and internal quotation marks omitted). The district court's conclusion that Danny Callahan would not have contracted polio "but for" the government's action thus goes only to the question of causation-in-fact, not proximate cause, because it does not answer the question of whether the particular result that occurred was a reasonable and probable consequence of the government's conduct. *See*

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have indicated that *Waffen* did not accurately articulate the contours of Maryland's proximate cause requirements. *See Hurley v. United States*, 923 F.2d 1091, 1096 (4th Cir.1991) ("Our interpretation of Maryland law in *Waffen* is called into question because we were interpreting Maryland law as espoused in *Hetrick v. Weimer*, which was later reversed by the Maryland Court of Appeals." (footnote omitted)); *Cooper v. Hartman*, 311 Md. 259, 533 A.2d 1294, 1297 & n. 4 (1987) (placing *Waffen* among a group of decisions that improperly "relaxed the standards regarding causation").

Callahan, 863 S.W.2d at 865 (Missouri courts "have generally said that the injury must be a reasonable and probable consequence of the act or omission of the defendant.").

The district court's explanation of why different results were required as to the claims against the government and Cyanamid, the vaccine manufacturer, suggests that the court believed the causation standard is different in cases where the duty arises under the Good Samaritan doctrine. The court stated:

> I find that Cyanamid cannot be held liable for contribution to SLU and that it is therefore entitled to summary judgment. While I recognize that this holding may seem asymmetrical, paradoxical, or even perverse in light of my finding that the government is liable for contribution, the difference in result flows from the difference in the nature of the respective duties owed by the United States and Cyanamid to those who were exposed to the live virus contained in OPV.
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> As indicated above, in *Sabin III* I ruled that the Good Samaritan doctrine and its parallel provision, *Restatement (Second) of Torts* § 323, imposed upon the government the duty not to approve vaccine seeds in violation of the OPV regulations. Cyanamid was under no such duty. Its duties and responsibilities to the members of the public, particularly to OPV recipients and their families, [are] defined by products liability law. In considering claims against Cyanamid, the focus must therefore be on the safety of its product, not the regulatory process for which the government bore responsibility. Likewise, in analyzing the element of proximate cause in claims against Cyanamid, the focus must be on whether the

> plaintiff can prove that it was a defect in the OPV that resulted in his injury, not simply—as in a case against the government—whether he had been exposed to OPV derived from a seed that had been improperly approved in violation of the regulatory process. Under Missouri law this element of causation is required whether a plaintiff sues for strict liability, negligence, or breach of warranty.

St. Louis Univ., 182 F.Supp.2d at 500. Missouri law, however, makes it quite clear that the Good Samaritan doctrine is relevant to the question of duty only; it has no effect on the general rules of causation. *See Wollen v. DePaul Health Center*, 828 S.W.2d 681, 683 (Mo.1992) (en banc) ("[T]his Court has recognized that section 323 [of the *Restatement (Second) of Torts*] creates a duty of care. In creating this duty, this section of the Restatement defines a type of negligent behavior but does not alter the rules of causation." (citation omitted)). Thus, SLU's claim against the government requires evidence of proximate cause in addition to evidence of but-for causation.

As to proximate cause, we note that all OPV, including OPV that satisfied all regulatory requirements, carried the risk that the recipient would actually contract polio. Therefore, to show that Danny's polio was caused by the government's regulatory violations, we conclude that SLU was required to establish that Danny likely would not have contacted polio (or would have contracted a less severe case of polio) from a vaccine that satisfied the government's neurovirulence requirements. Any lesser standard would result in the government being held strictly liable for its regulatory violations, which would be inconsistent with Missouri law. *See Sill v. Burlington No. R.R.*, 87 S.W.3d 386, 392 (Mo.Ct.App.2002) (explaining that the violation of a

statute can, under certain circumstances, support a negligence *per se* claim, but that the plaintiff must prove that the statutory "violation was the proximate cause of the injury."). And this evidence, of course, must be in the form of expert testimony. *See, e.g., Wright v. Barr,* 62 S.W.3d 509, 524 (Mo.Ct.App.2001) ("If there is a sophisticated injury, one that requires surgical intervention or other highly scientific techniques for diagnosis, expert medical testimony is required to prove causation.").

There is no such evidence in this record. At best, SLU's experts assumed that increased neurovirulence led to increased incidence of vaccine-associated polio, but SLU's experts did not offer that opinion. In fact, none of SLU's experts were even qualified to render such an opinion.[6] The district court recognized this absence of evidence, *see St. Louis Univ.,* 182 F.Supp.2d at 502 ("Whether or not an oral polio vaccine that complied with the OPV regulations would have caused Callahan and the plaintiffs in the other *Sabin* cases to contract polio ultimately is unknowable and unprovable."), as does SLU. SLU, however, insists that it is not required to present evidence of proximate cause.

According to SLU, the regulations establishing the neurovirulence standards created an "unrebuttable presumption" that any vaccine exceeding the standards posed an unacceptable risk that the recipient would contract polio. Brief of Appellee at 21. Thus, SLU contends

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[6] In the first appeal, this court noted that there was some evidence that a more neurovirulent vaccine caused Danny to have a more severe case of polio. SLU, however, did not pursue this theory after remand and does not pursue it on appeal. Moreover, the district court concluded that the expert who provided this testimony was not qualified to render an opinion on causation, and SLU does not challenge that determination on appeal.

that once it was established in the *Sabin* cases that the government violated its regulations and that the violations proximately caused the injuries, the government was automatically liable for the injuries suffered by anyone who received a vaccine derived from one of the vaccine seeds at issue in the *Sabin* cases. As noted above, such an approach is utterly inconsistent with Missouri law. *See Sill,* 87 S.W.3d at 392 ("If a submissible case is made under a negligence *per se* cause of action, a plaintiff could recover if a jury concluded that a statute was violated and the violation was the proximate cause of the injury."); *Friend v. Yokohama Tire Corp.*, 904 S.W.2d 575, 579 (Mo.Ct.App.1995) ("One of the elements of a negligence *per se* action is that the violation of a statute was the proximate cause of the injury.").

Because there is no evidence that the government's regulatory violations proximately caused Danny's injury, SLU has failed to show that it is entitled to contribution from the government. We therefore reverse the district court's grant of partial summary judgment in favor of SLU and we remand for the entry of judgment in favor of the government. *See Monahan v. County of Chesterfield, Va.*, 95 F.3d 1263, 1265 (4th Cir.1996) (explaining that where cross-motions for summary judgment have been filed, the appellate court can direct the entry of judgment in favor of the appellant).

REVERSED AND REMANDED.

LUTTIG, *Circuit Judge*, dissenting:

I would affirm the district court's judgment in this case under the binding precedent of the circuit. In *In re Sabin Oral Polio Vaccine Products Liability Litigation,*

984 F.2d 124 (4th Cir.1993) ("*Sabin IV*"), we determined that under a tort regime, identical in all relevant respects to the one at issue here, an injury, identical to the one at issue here, was proximately caused by tortious conduct identical to that alleged here. On the basis of the *reasoning* which we adopted in that case, I must conclude that our application here of Missouri state law yields the conclusion that appellee SLU proffered sufficient evidence to establish the legally necessary causation for it to prevail.

The majority reaches the opposite conclusion. It reasons that "our decision in *Sabin IV* [does not] serve as binding precedent in this case," *ante* at 300, because "the proximate cause determination in *Sabin III* was reached by applying Maryland and Florida law, while the proximate cause determination in this case must be made by applying Missouri law." *Ante* at 300. This reasoning would be compelling if SLU proposed that we apply the *state law holdings* of *Sabin IV* to the facts of the case before us today. But, the majority is wrong to suggest that SLU, or by implication, I, argue that *Sabin IV* is binding as a matter of Missouri state law. All that SLU asks, and all that I contend is appropriate, is that we reach our judgment by applying the binding *reasoning* of *Sabin IV.*

While our decision in *Sabin IV* resulted in state law holdings, it also produced reasoning, by which we reached those state law holdings. This reasoning is uniquely the creature of this court, and, as it is binding upon us, we must apply it in other cases involving the same predicate facts (*i.e.*, functionally identical underlying tort regime, facts, and causation theories). In this manner, *Sabin IV* binds us as a matter of federal law, delimiting the open field that we would otherwise face in formulating our reasoning. Because the question before

us is simply how we will reason to our application of Missouri's tort regime, which regime is functionally identical in the relevant regards to those from which we reasoned in *Sabin IV,* our conclusion as to how to reason to this application is governed by *Sabin IV.*

The majority, to its credit, does not attempt to deny the crucial point in this case, namely, that in *Sabin IV* we reasoned from two state tort law regimes, from injuries, and from asserted causation theories, that were functionally indistinguishable from those before us today. But, absent such a denial, it has no basis on which to reach the conclusion it reaches today other than that it disagrees with the reasoning we adopted in *Sabin IV.* While I am somewhat sympathetic to the critique the majority implicitly levels at that reasoning, the majority, as am I, is bound to abide by it until this court *en banc* or the Supreme Court holds otherwise.

Having mistakenly rejected the authority of *Sabin IV,* the majority asserts that the district court erred here because it engaged in no proximate cause determination whatsoever. But *Sabin IV* quite clearly shows the majority to be in error on this point. There, we concluded that an identical causation theory, in the unique circumstance where the tortfeasor's function is that of a product-approver, suffices to establish proximate cause. We reasoned as follows:

> The final point of appeal concerns the district court's determination that [the government's] *approval* of the lots was the *proximate cause* of [the plaintiff's] injuries. The test of probable [sic] cause is one of "reasonable probability or reasonable certainty." In other words, "the plaintiff has the burden of introducing evidence which affords a reasonable basis for the conclusion that it is more likely than

not that the conduct of the defendant was a substantial factor in bringing about the result."

The district court concluded:

> Regardless of the acceptability of the specific lots from which were derived the vaccine . . . if [the government] had properly applied 42 C.F.R. § 73.114(b)(1)(iii) . . . the seed would not have been used. This is so because the manufacturer would have been unable to satisfy the consistency requirement found in 42 C.F.R § 73.116(c). Likewise, regardless of the acceptability of the lots from which the vaccine administered to [the plaintiff] were derived, the lots would never have been produced and released but for the approval of [the] seed. . . . Thus, the causal connections between the regulatory violations and plaintiffs' injuries are logical, sensible and direct.
>
> The government's argument that the failure to amend the regulation was not the *proximate cause* of the plaintiff's injuries misconstrues the plaintiff's claims and the district court's opinion. [The government's] liability arose out of releasing vaccine in violation of the regulations, not in its failure to amend the regulations.

Sabin IV, 984 F.2d at 128 (emphasis added) (citations omitted).

By this passage, we clearly concluded that the district court's reasoning—what the majority here terms a merely but-for causation analysis—constituted a proper *proximate* cause analysis with respect to a tortfeasor who functions as a unilateral product-approver. Under this binding precedent, we are required to conclude that the

district court's identical reasoning here is likewise a proper proximate cause analysis.

The majority's underlying dissatisfaction with this analysis seems based on the belief that such an analysis "would result in the government being held strictly liable for its regulatory violations, which would be inconsistent with Missouri law." *Ante* at 303. As an initial matter, strict liability effects culpability standards (*e.g.*, negligence, recklessness, etc.), *not* causation standards. That every regulatory violation in the circumstance where the government is a product-approver is the proximate cause of injuries sustained by the use of the defectively approved product simply does not create strict liability since under Missouri law it still must be proven that the violation was the result of negligence or recklessness.

And, while I am somewhat sympathetic to the majority's other apparent concern—that the government is treated differently than the manufacturer with regards to the causal effect of its action in Callahan's injury—we may not base our judgment on it, for it is quite clear that we have already concluded that the district court's analysis, distinguishing between the two parties' causal effects, was proper. And this determination binds us, regardless of whether our prior reasoning as to why it is so is persuasive.

The majority's concern on this score, however, is not even fully borne out. That the causal effect of the government's conduct is differently understood than that of the manufacturer is the result of the fact that the government's role as tortfeasor here springs from its actions as a product-approver. As opposed to a manufacturer, who presumably sells a range of product, some with and some without defect, a product-approver's *only* role is to determine whether a particular product goes to market at

all. In this unique role, failure, and breach of a duty of care, does not result in any easy comparison between what would have happened had the defective "product" not been defective, because, for such a tortfeasor, the defective "product" is the failure to withhold *completely* the distributed item from distribution. Thus, had the government's "product" been free of defect, none of the offending vaccine would have been distributed at all. This contrasts with the case of a manufacturer who, had its product been defect free, would have distributed a defect free product. The causation of injury by one's "defective" action is quite different from the other, since one's "defect-free" action keeps all product from the market while the other instead distributes defect-free product. Since Florida and Maryland law, just like Missouri law, require plaintiffs to prove proximate cause by demonstrating that, had the product been defect-free, the injury would not have occurred, and since the government's defect-free product would have been the complete withholding of the vaccine, it was not too great of a stretch, even if not wholly persuasive, for us to conclude in *Sabin IV* that the alleged conduct proximately caused the alleged injury.

The district court's notation that its causation analysis took into account that the government acted under a Good Samaritan duty articulates this aspect of the case. That the majority instead thinks this notation signals that the lower court mistakenly "believed the causation *standard* is different in cases where the duty arises under the Good Samaritan doctrine[,]" *ante* at 302 (emphasis added), illustrates the panel's failure to appreciate how a manufacturer's defect causes injury in one way, while defective product approval causes injury in another. That different causal relationships exist between different categories of conduct and the injury they cause bespeaks

nothing as to what legal standard applies to those causal relationships in a tort action.

But even if there were any merit to the majority's concerns that our prior analysis effectively creates a strict liability culpability standard or a but-for causation standard and treats the government differently from the manufacturer, those issues have already been fought over and decided—and not by today's opinion. *Sabin IV* decided the matter and so provides binding reasoning, which, if we were to apply it today, would result in affirmance of the district court's judgment. Indeed, the rule we face not only binds us, but also every district court within our circuit and every future panel of our court, and the dissent's judgment only evades that reality temporarily. *See Booth v. Maryland*, 327 F.3d 377, 382-83 (4th Cir.2003) (explaining that it is error to follow the more recent of two contradicting panels).

For these reasons, I respectfully dissent.

UNITED STATES DISTRICT COURT
D. MARYLAND

Nos. CIV.JFM-95-CV-3639,
CIV.JFM-99-CV-1316

January 25, 2002

ST. LOUIS UNIVERSITY,

Plaintiff,

—v.—

THE UNITED STATES,

Defendant.

AMERICAN CYANAMID CO.,

Plaintiff,

—v.—

ST. LOUIS UNIVERSITY,

Defendant.

Raymond F. Altman, Baltimore, MD, Marc S. Moller, Henry Gluckstern, Kreindler & Kreindler, New York City, Rex Carr, Carr, Korein, East St. Louis, IL, Stanley

P. Kops, Kops & Fenner, Philadelphia, PA, P. Terrence Crebs, Herzog, Crebs & McGhee, St. Louis, MO, *for St. Louis University.*

Perry F. Sekus, Lynne A. Battaglia, U.S. Attorneys Office, Baltimore, MD, Mary McElroy Leach, Frank Hunger, U.S. Dept. of Justice, Washington, DC, *for U.S.*

Roger W. Yoerges, Wilmer, Cutler and Pickering, Washington, DC, David P. Donovan, Wilmer Cutler and Pickering, Tysons Corner, VA, *for American Cyanamid Co.*

MEMORANDUM

MOTZ, *District Judge.*

These two related cases may be the last involving the Sabin oral polio vaccine that was the subject of MDL proceedings before me. *See In re Sabin Oral Polio Vaccine Prod. Liab. Litig.*, 743 F.Supp. 410 (D.Md.1990) ("*Sabin I*"); 763 F.Supp. 811 (D.Md.1991) ("*Sabin II*"); 774 F.Supp. 952 (D.Md.1991) ("*Sabin III*"). They arise from a $16 million judgment obtained by Danny Callahan in a medical malpractice action instituted against St. Louis University ("SLU") in Missouri. After the judgment was affirmed on appeal by the Missouri Supreme Court, SLU instituted an action against the United States in this court for contribution, contending that the paralysis from which Callahan suffers was caused by his having been administered a dose of vaccine derived from a seed I found in the MDL proceedings to have been wrongfully approved by the government. SLU instituted a similar action in Missouri against American Cyanamid ("Cyanamid"), the parent of Lederle Laboratories, the manufacturer of the vaccine. SLU eventually consented

to the dismissal of that action after extensive discovery had been conducted. In April 1999, I granted a motion for summary judgment in favor of the United States against SLU. In the wake of that decision, Cyanamid filed a declaratory action against SLU, and I entered summary judgment in its favor as well. SLU appealed from both decisions. The Fourth Circuit reversed my rulings and remanded the cases for further proceedings.

Although no further discovery has been conducted after remand, the parties have agreed that renewed summary judgment motions are appropriate. In its action against the United States, SLU has moved for partial summary judgment on the issues that the government was negligent and that its negligence was at least one of the proximate causes of Callahan's paralysis. The United States also has requested summary judgment. Similarly, Cyanamid has filed a summary judgment motion in its declaratory judgment action against SLU.

I.

The relevant background facts concerning the underlying *Callahan* action, the *Sabin* MDL proceedings, and the prior history of SLU's contribution action against the United States were succinctly stated by the Fourth Circuit in its opinion reversing my ruling in the case against the United States. 5 Fed.Appx. 133, 136-37 (4th Cir. 2001). That opinion was not published in the Federal Reporter, and I will take the liberty of quoting from it verbatim:

> A. The State Court Action
>
> In 1978, three-month-old Danny Callahan received a dose of Orimune, an oral vaccine containing an attenuated strain of a live polio virus. Approxi-

mately one month later, Danny developed a perirectal abscess that was treated by employees of Cardinal Glennon Hospital and SLU. The abscess was not drained and no culture was taken to determine if the infection was caused by gram positive or gram negative bacteria. Danny was given an antibiotic that was effective only on gram positive bacteria. After several days, Danny's condition had not improved, and his mother noticed that his legs appeared to be "floppy." His parents took him back to the hospital, where the abscess was incised and drained. Cultures of the abscess revealed four types of gram negative bacteria, and Danny was given an antibiotic that was effective against those organisms. Although the abscess improved, Danny's legs and left arm remained paralyzed. Type III polio virus (the type in the vaccine dose he had received) was isolated in Danny's stool, and, although some experts disagree, it appears that Danny suffers from vaccine-associated polio.

The Callahans filed a medical malpractice action against SLU, Cardinal Glennon, and American Cyanamid Company, parent company of the manufacturer of the vaccine. At the time of trial, only SLU and Cardinal Glennon remained as defendants. The Callahans' expert witnesses testified that Danny's paralysis was caused by the negligence of SLU and Cardinal Glennon in failing to treat the abscess properly when Danny was first brought to the hospital. According to the experts, the improper treatment allowed endotoxins to be released, which suppressed Danny's immune system. Because Danny's immune system was compromised, the attenuated polio virus contained in the vaccine was able to replicate fast enough to overcome his sup-

pressed immune system, resulting in poliomyelitis. The Callahans' experts testified that if the abscess had been treated properly from the outset, the endotoxins would not have been released, his immune system would not have been suppressed, and he would not have contracted polio.

SLU and Cardinal Glennon, however, presented evidence that Danny's paralysis was not connected to the abscess and that it was caused by the attenuated polio virus in the vaccine mutating to a virulent form after it had been ingested. They presented evidence showing that in the 1980s approximately one in four hundred thousand people receiving Orimune developed polio. Their experts also testified that the Callahans' theory that endotoxins suppress the immune system making a host more susceptible to vaccine-induced poliomyelitis was not supported by any known research.

The jury returned a $16 million verdict against SLU and Cardinal Glennon. After the trial, Cardinal Glennon entered into a settlement agreement with the Callahans. SLU appealed, and the jury's verdict was affirmed by the Missouri Supreme Court sitting en banc. *See Callahan v. Cardinal Glennon Hosp.*, 863 S.W.2d 852 (Mo.1993) (en banc).

B. *In re Sabin*

While the *Callahan* case was winding its way through the Missouri court system, multi-district Orimune cases filed against the United States government under the Federal Tort Claims Act were transferred to the District of Maryland for resolution of the common legal and factual questions. . . .

> The plaintiffs in the *In re Sabin* cases contracted polio after receiving a Type III Orimune vaccine or after coming into contact with a recipient of the Type III vaccine. They sued the government, alleging, inter alia, that the National Institute of Health's Division of Biologic Standards negligently issued a license to Lederle Laboratories (a subsidiary of American Cyanamid) to manufacture the vaccine and improperly approved vaccine that did not meet the "neurovirulence" standards set forth in the governing regulations. The district court ultimately concluded that the government violated the governing regulations and was negligent in approving certain vaccine "seeds" and the release of lots derived therefrom and that its negligence was a proximate cause of the injuries suffered by the plaintiffs, who received or were exposed to vaccines from lots derived from the improperly approved seeds. *See* 774 F.Supp. at 957-58, 763 F.Supp. at 821-25. The district court's *Sabin* opinions were affirmed by this Court on appeal. *See In re Sabin Oral Polio Vaccine Prod. Liab. Litig.*, 984 F.2d 124 (4th Cir.1993) (per curiam). The Orimune vaccine received by Danny Callahan was derived from one of the vaccine seeds that the *In re Sabin* cases concluded were improperly approved by the government. . . .

5 Fed.Appx. at 136-37.

II.

After stating these background facts, the Fourth Circuit went on to decide that I erred in holding that under Missouri law (which undisputably is applicable here) the findings adverse to SLU in the *Callahan* case would have a collateral estoppel effect in a subsequent contri-

bution action. In effect, the Fourth Circuit held that SLU was free to present in a contribution action the defense it had lost in *Callahan*, i.e., that its alleged malpractice in improperly treating Callahan's abscess was immaterial because known research does not support the opinion expressed by Callahan's experts that endotoxins suppress the immune system, making a host more susceptible to vaccine-induced polio.

SLU acknowledges that the invalidity of the immunosuppression theory has not yet been established in this case, and it is not moving for complete summary judgment on the ground that its own negligence was *de minimis* or nil. It is seeking only a ruling that the United States was negligent and that the negligence was at least one of the proximate causes resulting in Callahan's paralysis. The United States has agreed to be bound in this litigation by the regulatory violations that were found to exist in *Sabin II*. (United States' Opp'n at 2.) It also has stipulated to owing a duty of care to Callahan.[1] (*Id.* at 15.) Although it stipulates to duty and to the regulatory violations, the United States does not admit to proximate cause.

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[1] In *Sabin III*, I applied the Good Samaritan doctrine of the Restatement (Second) of Torts § 324A (1965) as the source of the duty the government owed to the plaintiffs, parents who had contracted polio from shed virus after their children were administered vaccine. 774 F.Supp. at 954. I noted that in cases, such as this one, in which persons contracted polio as the result of vaccine administered directly to them, the source of duty is found in a parallel provision, Restatement (Second) of Torts § 323 (1965). *Id.* at 954 n. 5. That provision covers situations in which a tortfeasor renders services to another and, by failing to exercise reasonable care, causes injury to that person. *See id.* Missouri has adopted § 323 as part of its tort law. *See Stanturf v. Sipes*, 447 S.W.2d 558, 561-62 (Mo.1969); *Strickland v. Taco Bell Corp.*, 849 S.W.2d 127, 132 (Mo.Ct.App.1993).

In my original opinion I found that "none of SLU's experts have expressed an opinion that, if Callahan had been given a vaccine that satisfied the neurovirulence requirements of the applicable regulations, he would not have contracted polio."[2] SLU has not supplemented the record on this point in any respect, and I adhere to that finding. The United States contends that the absence of any such opinion is fatal to SLU's claims since in order to establish proximate cause, SLU must prove that Callahan contracted polio as the result of excessive neurovirulence in vaccine derived from a seed that had been wrongfully approved. Stated conversely, according to the United States, SLU must prove that vaccine derived from a seed meeting regulatory requirements would not have had the same effect as did the vaccine that Callahan received.

The United States made a similar argument in *Sabin III*, and I found it unpersuasive. I held that proximate cause was established by the mere fact that "if . . . [seeds 45 B 85 and 45 B 165[3] had not been in use, the

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[2] In its initial opinion the Fourth Circuit held that this finding was erroneous because Robert Baltimore, one of SLU's experts, had "stated that, in his opinion, an excessively neurovirulent vaccine would produce more severe paralysis than would a vaccine that complied with all regulatory requirements." However, on April 25, 2001, after the United States filed a petition for clarification or rehearing pointing out that SLU had represented that it was not offering Dr. Baltimore as an expert on neurovirulence, the court issued an order stating that "the panel opinion should not be construed as determining the admissibility of any expert testimony. The District Court is free to consider *de novo* any evidentiary issues that might be raised on remand." SLU has not attempted to broaden the area of Dr. Baltimore's proffered expertise. Therefore, I continue to find, as I did originally, that nothing he has opined is sufficient to establish that a vaccine complying with the regulations would not have caused Callahan to contract polio.

[3] The vaccine administered to Callahan was derived from seed 45 B 85.

vaccine giving rise to the injuries would not have been manufactured. The evidence clearly establishes that but for . . . [the United States's] negligence, the seeds would not have been used." 774 F.Supp. at 958. I went on to reject an ancillary contention made by the government that proximate cause was dispelled by the fact that the specific lots involved in the two cases under consideration had met the regulatory neurovirulence criteria, and I concluded that "the causal connection between the regulatory violations and plaintiffs' injuries are logical, sensible and direct." *Id.* The Fourth Circuit affirmed this holding on appeal.

My reasoning in *Sabin III* is equally applicable here.[4] This can be most easily seen by hypothesizing that SLU is correct in contending that the immunosuppression allegedly caused by its malpractice played absolutely no role in making Callahan susceptible to contracting polio from OPV. If that is true, Callahan stands in exactly the same position as did the plaintiffs in other *Sabin* cases because in that event the sole cause of his polio was the vaccine. Likewise, even if the immunosuppression did play some role in the disease process, Callahan's expo-

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[4] It might appear that I am modifying the view I originally took in this case that SLU's case was critically flawed by the absence of evidence that a less virulent vaccine would not have caused Callahan's paralysis. The context in which I expressed that view was, however, substantially different from the one now presented. As I have already indicated, in my original opinion I held that my collateral estoppel ruling foreclosed SLU from relying on the opinion of its experts that it had not been negligent at all and that the Orimune administered to Callahan had been the sole cause of his polio. I further found that because of that holding the only way that SLU could prevail would be to render its own negligence immaterial by proving that a less neurovirulent vaccine would not have caused a person in an immunosuppressed state to contract polio. The Fourth Circuit's decision has mooted this line of reasoning.

sure to the oral vaccine had to be a contributing cause to his paralysis. The isolation of Type III polio virus in Callahan's stool demonstrates he contracted polio, and no one suggests that the immunosuppression alone could have caused the disease. Accordingly, as I held in *Sabin III*, Callahan was exposed to the virus as a consequence of the government's violation of the OPV regulations. If the government had not wrongfully approved the seed from which the vaccine was derived, Callahan would never have been administered a dose of Orimune and would never have contracted polio even if he had been immunosuppressed. This "but for" relationship meets the standard of proximate cause under Missouri law just as it does under the law of Maryland and Florida applicable in *Sabin III*. *See Callahan*, 863 S.W.2d at 860-61 (explaining that "but for" causation means that " 'the defendant's conduct is a cause' of the event if the event would not have occurred 'but for' that conduct") (*quoting Prosser and Keeton on Torts* § 41 (5th ed.1984)); *Martin v. City of Washington*, 848 S.W.2d 487, 493 (Mo.1993) (en banc) (describing the "simplest test for proximate cause" as "whether the facts show that the injury would not have occurred in the absence of the negligent act"); *Bauman v. Conrad*, 342 S.W.2d 284, 287 (Mo.Ct.App.1961) ("The proof must show that had the negligence not occurred, the . . . plaintiff's injuries would not have occurred.").[5]

For these reasons, I find that the United States is liable in contribution because its violations of its own regula-

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[5] I should point out that in ruling against the United States on this issue, I am not relying upon the doctrine of collateral estoppel, which may not be invocable against the government. *See United States v. Mendoza*, 464 U.S. 154, 162, 104 S.Ct. 568, 78 L.Ed.2d 379 (1984). I am simply following my reasoning in *Sabin III* that was affirmed on appeal.

tions constituted negligence and were a proximate cause of Callahan's paralysis. I am not making any determination as the extent of that liability. If I ultimately conclude that Callahan likely would not have contracted polio but for SLU's failure to make a proper diagnosis and treatment of his abscess, SLU will be subject to a substantially greater share of liability than the United States. If, on the other hand, Callahan's immunosuppression was, as SLU contends, merely coincidental and not a material factor in causing him to contract polio, the greater share of liability will fall upon the United States. Resolution of these issues must await the development of a full factual record.

III.

I will now turn to the issues raised by Cyanamid's declaratory judgment action. I find that Cyanamid cannot be held liable for contribution to SLU and that it is therefore entitled to summary judgment. While I recognize that this holding may seem asymmetrical, paradoxical, or even perverse in light of my finding that the government is liable for contribution, the difference in result flows from the difference in the nature of the respective duties owed by the United States and Cyanamid to those who were exposed to the live virus contained in OPV.

As indicated above, in *Sabin III* I ruled that the Good Samaritan doctrine and its parallel provision, Restatement (Second) of Torts § 323, imposed upon the government the duty not to approve vaccine seeds in violation of the OPV regulations. Cyanamid was under no such duty. Its duties and responsibilities to the members of the public, particularly to OPV recipients and their families, is defined by products liability law. In

considering claims against Cyanamid, the focus must therefore be on the safety of its product, not the regulatory process for which the government bore responsibility. Likewise, in analyzing the element of proximate cause in claims against Cyanamid, the focus must be on whether the plaintiff can prove that it was a defect in the OPV that resulted in his injury, not simply—as in a case against the government—whether he had been exposed to OPV derived from a seed that had been improperly approved in violation of the regulatory process. Under Missouri law this element of causation is required whether a plaintiff sues for strict liability, negligence, or breach of warranty. *See, e.g., Bone v. Ames Taping Tool Sys., Inc.*, 179 F.3d 1080, 1081 (8th Cir.1999) ("Under Missouri law, to prevail on a claim of strict liability, negligence, or breach of warranty, [plaintiff] must prove that his use of the [defendant's product] directly caused or contributed to cause some or all of his injuries."); *Chism v. W.R. Grace & Co.*, 158 F.3d 988, 991 (8th Cir.1998) (explaining that for negligence or strict liability claims under Missouri law, a plaintiff must establish a causal connection between the defendant's conduct and the plaintiff's injury); *Nesselrode v. Executive Beechcraft, Inc.*, 707 S.W.2d 371, 375-76 (Mo.1986) (en banc) (holding that the plaintiff in a strict liability product defect case must show that the defect caused his injuries); *Mothershead v. Greenbriar Country Club, Inc.*, 994 S.W.2d 80, 89 (Mo.Ct.App.1999) (requiring proof of causal link between product defect and injury in failure to warn case).

Product safety regulations certainly may provide a reference point in defining the standard of conduct a manufacturer must meet in fulfilling its duty to consumers

under products liability law.[6] Likewise, violations of safety regulations may subject a manufacturer to governmental enforcement action, including criminal prosecution under appropriate circumstances. However, such violations do not provide themselves provide a basis for a private right of action independent of general tort principles. *See In re Orthopedic Bone Screw Prod. Liab. Litig.*, 193 F.3d 781, 791-92 (3d Cir.1999). Moreover, although I recognize that at least one court has concluded to the contrary, *see Campagna v. American Cyanamid Co.*, 337 N.J.Super. 530, 767 A.2d 996 (2001), I am of the view that violation of the OPV regulations is not sufficient to prove the element of proximate cause in a context, such as that presented by SLU's claims against Cyanamid, where a plaintiff must prove that it is more likely than not that it was excessive neurovirulence in a dose of vaccine that caused him to contract polio. The regulatory criteria were developed entirely from monkey neurovirulence tests and, as the absence of any proffered expert testimony by SLU affirms, the results of those tests alone are not sufficient

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[6] It might be noted that in this case reference solely to the literal language of the OPV regulations as setting the substantive standard of care in a products liability action would be problematical since the persons responsible for enforcement of the regulations (including some of the best scientists in the United States) had concluded that the safety standards the regulations embodied were unreasonably high. Indeed, that was the very reason they approved seeds whose test results did not meet the strict regulatory criteria. Likewise, the fact that the OPV regulations have been abolished is a factor than could be considered in determining whether Orimune was defective. *See* Restatement (Third) of Torts § 4 cmt. d (1998) ("When repeal or invalidation [of a statute or regulation] takes place post-injury, but prior to adjudication, the court may take the repeal or invalidation into account in deciding whether noncompliance with the statute or regulation renders the product defective.")

to establish a causal connection between a particular individual's contraction of polio, on the one hand, and the marginal difference in neurovirulence between vaccine derived from a seed compliant with the OPV regulations and vaccine developed from a non-compliant seed, on the other.[7]

On the surface this holding might appear to contradict the statement I made in *Sabin III* that "it must be concluded that by releasing vaccine lots whose monkey neurovirulence test results exceeded the regulatory criteria, DBS increased the risk of harm to persons who were vaccinated and . . . exposed to the shed virus." 774 F.Supp. at 955. However, in *Sabin III* I was not considering the issue of whether a dose of Orimune had been a proximate cause of a particular individual's paralysis: an inquiry which, under products liability law, requires proof of a causative connection between the paralysis and a defect in Orimune. Rather, I was addressing the question of whether by approving seeds not compliant with the OPV regulations, the United States had breached its duty to the members of the public, which it had assumed by virtue of its undertaking to regulate a potentially hazardous condition for the benefit of others. Resolution of that question required me to determine whether the United States had "increase[d] the risk of . . . harm" to those who were vaccinated or otherwise exposed to the live polio virus within the meaning of

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[7] If the vaccine lot from which the Orimune administered to Callahan itself passed the criteria set by the OPV regulations, a matter the parties appear to dispute, that would pose an additional obstacle to SLU's proof in this case. Although, as noted previously in the text and explained in *Sabin III*, 774 F.Supp. at 958, this fact is not relevant to the proximate cause analysis in a case against the United States, it might be fatal to a claim against Cyanamid, even if the claim were otherwise viable.

§ 24A of the Restatement (Second) of Torts.[8] In making that determination, I found that the neurovirulence criteria of the OPV regulations—which the government itself had adopted—provided "the best available scientific standard" for determining potential excessive neurovirulence and that the government had therefore increased the risk of harm to the public. *Id.*

I did not find, however, that Orimune was, in fact, excessively neurovirulent when administered to humans or that an OPV meeting the regulatory criteria would not have equally caused the *Sabin III* plaintiffs to contract polio. Once I found that the United States had breached its duty by increasing the risk of harm to the public, the only proximate causal connection I found necessary to make was the one established by the essential fact that if seed 45 B 85 (and seed 45 B 165) had not been improperly approved, the vaccine to which the *Sabin III* plaintiffs were exposed would never have been put into use. *Id.* at 958.

Several final comments, somewhat reiterative though they are, perhaps are in order to explain why I am holding the United States, but not Cyanamid, liable for contribution. Whether or not an oral polio vaccine that complied with the OPV regulations would have caused

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[8] The *Campagna* court, in quoting the language in question, recognized that I was not analyzing the element of proximate cause but was rather "[c]ommenting on an issue closely akin" to it. 767 A.2d at 1003. The accuracy of this reading is confirmed by the fact that the quoted language appears in the section of my opinion entitled "Existence of Duty," not the section entitled "Proximate Cause." Moreover, I prefaced my statement with the observation (based upon the evidentiary record) that "there is no necessary or definitive correlation between the results of monkey neurovirulence tests and a vaccine's neurovirulence when administered to humans. . . ." 774 F.Supp. at 955.

Callahan and the plaintiffs in the other *Sabin* cases to contract polio ultimately is unknowable and unprovable. What is known, or at least that which I found to be demonstrated by the record in the MDL cases, is that the OPV program "has resulted in the virtual eradication of wild poliovirus in the Western Hemisphere," that it was "perhaps the most successful public health program in history," and that the OPV manufactured by Lederle "has always been 'state of the art.' " *Sabin II*, 763 F.Supp. at 813. This combination of the unknowable and the known make it impossible for SLU to prevail on a claim against Cyanamid since, as I have indicated, such a claim, arising solely under products liability law, requires proof that a product defect caused the plaintiff to suffer injury.

The claim against the United States, however, turns on a more fundamental principle: the necessity of upholding the rule of law. In *Sabin II* I found that although the officials responsible for the establishment and implementation of the OPV program were "extraordinarily able professionals who consistently acted in the public interest as they reasonably perceived it to be," 763 F.Supp. at 813, I also found in *Sabin III* that they "arrogated to themselves the power to define what constituted an acceptable [public health] risk." 774 F.Supp. at 957. They purposely decided not to amend the regulations embodying the neurovirulence criteria they originally deemed proper because they believed that considerations of health policy so required. I have never questioned the subjective good faith of those officials or, indeed, the objective reasonableness of their decision from a public health perspective. But in taking the actions they did, they increased the risk that several more individuals would contract polio as a result of exposure to OPV than would have done so if the OPV regulations had been strictly followed. It may well be that the rest of us were

beneficiaries of a resultant harm suffered by a few. For that very reason, it is proper that we collectively be held liable for our government's actions.

A separate order effecting the rulings in this memorandum is attached.

ORDER

For the reasons stated in the accompanying memorandum, it is, this 25th day of January 2002, ORDERED that:

1. Plaintiff's Motion for Partial Summary Judgment in *St. Louis University v. United States* is granted.

2. Plaintiff's Motion for Summary Judgment in *American Cyanamid Co. v. St. Louis University* is granted.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Civil No. JFM-95-3639

ST. LOUIS UNIVERSITY

—v.—

UNITED STATES OF AMERICA

ORDER

In accordance with the directive of the United States Court of Appeals for the Fourth Circuit, it is, this 12th day of September 2003

ORDERED

1. The motion of the United States for summary judgment is granted; and

2. Judgment is entered in favor of the United States of America against St. Louis University.

/s/
J. FREDERICK MOTZ
United States District Judge

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

Filed August 12, 2003

No. 02-1351
CA-95-3639-JFM

ST. LOUIS UNIVERSITY, a corporation,

Respondent,

—v.—

UNITED STATES OF AMERICA,

Petitioner.

On Petition for Rehearing En Banc

The respondent's petition for rehearing en banc was submitted to this Court. As no member of this Court requested a poll on the petition for rehearing en banc,

IT IS ORDERED that the petition for rehearing en banc is denied.

For the Court,

/s/ PATRICIA S. CONNOR
CLERK

42 C.F.R. § 73.100, et. seq.

(a) *Proper name and definition.* For the purpose of section 351(a)(2) of the act and § 73.1(k), the proper name of this product shall be "Poliovirus Vaccine, Live, Oral," followed by a designation of the form in which the vaccine is distributed by the manufacturer. The vaccine shall be a preparation of one or more live, attenuated polioviruses grown in monkey kidney cell cultures, prepared in a form suitable for oral administration.

(b) *Criteria for acceptable strains and acceptable seed virus.* (1) Strains of attenuated poliovirus Types 1, 2 and 3 used in the manufacture of the vaccine shall be identified by: (i) Historical records including origin and techniques of attenuation, (ii) antigenic properties, (iii) neurovirulence for monkeys, (iv) pathogenicity for other animals and tissue cultures or various cell types, and (v) established virus markers including rct/40, d, MS.

(2) Poliovirus strains shall not be used in the manufacture of Poliovirus Vaccine, Live, Oral, unless (i) data are submitted to the Surgeon General which establish that each such strain is free of harmful effect, upon administration in the recommended dosage to at least 100,000 people susceptible to poliomyelitis, under circumstances which were adequate epidemiological surveillance of neurological illness has been maintained, and, (ii) each such strain produces a vaccine meeting the safety and potency requirements of §§ 73.114(b), 73.115, and 73.117. Susceptibility shall be demonstrated by blood tests, stool examinations and other appropriate methods.

(3) Each seed virus used in manufacture shall be demonstrated to be free of extraneous microbial agents.

(4) No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the NIH Reference Attenuated Poliovirus. The neurovirulence of the seed virus shall be demonstrated by the following tests to be performed by the manufacturer: (i) The test prescribed in § 73.114(b)(1) using seed virus as test material in place of monovalent virus pool material and (ii) the following comparative intramuscular neurovirulence test: Each of at least ten monkeys shall be injected with a total of 5.0 ml. of the seed virus under test in one or more proximate locations of either a gluteus or gastrocnemius muscle. Similar injections shall be made in another group of ten monkeys using the NIH Reference Attenuated Poliovirus. Each monkey shall be injected intramuscularly with no less than 10 TCID of viral inoculum. All monkeys shall be observed for 17 to 21 days and a comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the NIH Reference Attenuated Poliovirus, as prescribed in § 73.144(b)(1)(iii).

(5) Subsequent and identical neurovirulence tests shall be performed in monkeys whenever there is evidence of a charge in the neurovirulence of the production virus and upon introduction of a new production seed lot and as often as necessary otherwise to establish to the satisfaction of the Surgeon General that the seed virus strains for vaccine manufacture have maintained their neurovirulence properties as set forth in § 73.114(b)(1).

(6) The Surgeon General may, from time to time, prohibit the use a specified strain whenever he finds it is practicable to use other strain of the same type which is potentially less pathogenic for man, and that it will produce a vaccine of equivalent safety and potency.

§ 73.111 NIH reference strains.

The following NIH reference viruses shall be obtained from the Division of Biologics Standards.

NIH Reference Poliovirus, Live Attenuated, Type 1, as a control for correlation of virus titers in tissue cultures.

NIH Reference Poliovirus, Live Attenuated, Type 2, as a control for correlation of virus titers in tissue cultures.

NIH Reference Poliovirus, Live Attenuated, Type 3, as a control for correlation of virus titers in tissue culture.

NIH Reference Attenuated Poliovirus, Type 1, as a control for correlation of monkey neurovirulence tests.

§ 73.112 Animal conditioning, personnel, and facilities.

(a) *Monkey conditioning, housing and handling.* (1) Only Macaca monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable, in overt good health, that have reacted negatively to tuberculin at the start of the prescribed quarantine period, shall be used as the source of kidney tissue for the manufacture of poliovirus vaccine.

(2) Monkeys that have been used previously for experimental purposes shall not be used as a source of kidney tissue in the manufacture of vaccine.

(3) Monkeys to be used as a source of kidney tissue in vaccine manufacture shall be maintained in quarantine for at least six weeks prior to use in cages closed on all

sides with solid materials except the front, which shall be screened. Not more than two monkeys shall be housed in one cage, and cage mates shall not be interchanged.

(4) Excluding deaths from accidents or causes not due to infectious diseases, if the death rate of any group of monkeys being conditioned in accordance with subparagraph (3) of this paragraph exceeds five percent per month, the remaining monkeys may be used for poliovirus vaccine only if they survive a new quarantine period.

(5) Each animal at necropsy shall be examined under the direction of a qualified pathologist, physician, or veterinarian, having experience with diseases of monkeys for the presence of signs or symptoms of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums and (iii) signs of conjunctivitis. If there are any such signs, or other significant gross pathological lesions, the kidneys shall not be used in the manufacture of vaccine.

(b) *Personnel.* All possible steps shall be taken to insure that personnel involved in processing the vaccine are immune to poliovirus in order to minimize the possibility that they may become excretors of poliovirus.

(c) *Facilities.* The space set aside for work with live poliovirus vaccine shall not be sued for any other purpose during the vaccine processing period. All areas used for live poliovirus vaccine processing shall be decontaminated prior to the initiation of such processing. Test procedures which potentially involve the presence of micro-organisms including viruses other than the vaccine strains, or the use of tissue culture cell lines other

than primary cultures, shall not be conducted in live poliovirus vaccine manufacturing areas.

§ 73.113 Manufacture of poliovirus vaccine, live, oral.

(a) *Primary cell cultures.* Only primary monkey kidney tissue cultures may be used in the manufacture of poliovirus vaccine. Continuous line cells shall not be introduced or propagated in vaccine manufacturing areas.

(b) *Virus passages.* Virus in the final product shall represent no more than five tissue culture passages from the original strain each of which shall have met the criteria of acceptability prescribed in § 73.110(b).

(c) *Identification of processed kidneys.* The kidneys from each monkey shall be processed and the viral fluid resulting therefrom shall be identified as a separate monovalent harvest and kept separately from other monovalent harvests until all samples for the tests prescribed in the following paragraph relating to that pair of kidneys shall have been withdrawn from the harvest.

(d) *Monkey kidney tissue production vessels prior to virus inoculation.* Prior to inoculation with the seed virus, the tissue culture growth in vessels representing each pair of kidneys shall be examined microscopically for evidence of cell degeneration at least three days after complete formation of the tissue sheet. If such evidence is observed, the tissue from that pair of kidneys shall not be used for poliovirus vaccine manufacture. To test the tissue found free of cell degeneration for further evidence of freedom from demonstrable viable microbial agents, the fluid shall be removed from the cell cultures immediately prior to virus inoculation and tested in each

of four culture systems: (1) Macaca monkey kidney cells; (2) Cercopithecus monkey kidney cells, (3) primary rabbit kidney cells, and (4) human cells (from one of the systems described in § 73.114(a)(6), in the following manner: Aliquots of fluid from each vessel shall be pooled and at least ten ml. of the polio inoculated into each system, with ratios of inoculum to medium being 1:1 to 1:3 and with the area of surface growth of cells at least three square centimeters per milliliter of test inoculum. The cultures shall be observed for at least 14 days. If these tests indicate the presence in the tissue culture preparation of any viable microbial agent the tissue cultures so implicated shall not be used for poliovirus vaccine manufacture.

(e) *Control vessels.* Before inoculation with seed virus, sufficient tissue culture vessels to represent at least 25 percent of the cell suspension from each pair of kidneys shall be set aside as controls. The control vessels shall be examined microscopically for cell degeneration for an additional 14 days. The cell fluids from such control vessels shall be tested, both at the time of virus harvest and at the time of virus harvest and at the end of the additional observation period, by the same method prescribed for testing of fluids in the preceding paragraph (d) of this section. In addition, the cell sheet in each control vessel shall be examined for presence of hemadsorption viruses by the addition of guinea pig red blood vessels.

(f) *Virus harvest; interpretation of test results.* At least 80 percent of the control vessels shall successfully complete the additional 14-day observation period without microscopic evidence of cell degeneration of the tissue sheets. If less than 80 percent of the control vessels fail to complete satisfactorily the observation period, no tis-

sue from the kidneys implicated shall be used for poliovirus vaccine manufacture. If the test results of the control vessels indicate the presence of any extraneous agent at the time of virus harvest, the entire virus harvest from that tissue culture preparation shall not be used for poliovirus vaccine manufacture. If any of the tests or observations described in paragraph (d) or (e) of this section demonstrate the presence in the tissue culture preparation of any microbial agent known to be capable of producing human disease, the virus grown in such tissue culture preparation shall not be sued for poliovirus vaccine manufacture.

(g) *Kidney tissue production vessels after virus inoculation-temperature.* After virus inoculation, production vessels shall be maintained at a temperature not to exceed 350? C during the course of virus propagation.

(h) *Kidney tissue virus harvests.* Virus harvested from vessels containing the kidney tissue from one monkey may constitute a monovalent virus pool and be tested separately, or viral harvests from more than one pair of kidneys may be combined, identified and tested as a monovalent pool. Each pool shall be mixed thoroughly and samples withdrawn for testing as prescribed in § 73.114(a). The samples shall be withdrawn immediately after harvesting and prior to further processing, except that samples of test materials frozen immediately after harvesting and maintained at -60? C or below, may be tested upon thawing, provided no more than one freeze-thaw cycle is employed.

(i) *Filtration.* After harvesting and removal of samples for the safety tests described in § 73.114(a), the pool shall be passed through sterile filters having a sufficiently small porosity to assure bacteriologically sterile filtrates.

§ 73.114 Test for safety.

(a) *Tests prior to filtration.* Monovalent virus pools shall contain no demonstrable viable microbial agent other than the attenuated live polioviruses intended. The vaccine shall be tested for the absence of adventitious and other infectious agents including polioviruses of other types or strains, simian agents, Mycobacterium tuberculosis, pox viruses, lymphocytic chorlomeningitis virus, Echo viruses, Coxsackie viruses and B-virus. Testing of each monovalent pool shall include the following procedures:

(1) *Inoculation of rabbits.* A minimum of 100 ml. of each monovalent virus pool shall be tested by inoculation into at least ten healthy rabbits, each weighing 1500-2500 grams. Each rabbit shall be injected intradermally in multiple sites, with a total of 1.0 ml. and subcutaneously with 9.0 ml. of the viral pool, and the animals observed for at least three weeks. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool may be used for poliovirus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of B-virus or any other viral infection.

(2) *Inoculation of adult mice.* Each of at least 20 adult mice each weighing 15-20 grams shall be inoculated intraperitoneally with 0.5 ml. and intracerebrally with 0.03 ml. of each monovalent virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection by direct observation and subinocula-

tion of appropriate tissue into at least 5 additional mice which shall be observed for 21 days. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of lymphocytic choriomeningitis virus or other viral infection.

(3) *Inoculation of suckling mice*. Each of at least 20 suckling mice less than 24 hours old, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 0.1 ml. of the monovalent virus pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness shall be necropsied and all areas examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least live suckling mice by the intracerebral and intraperitoneal routes and daily observed for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14 day test. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of Coxsackie or other viral infection.

(4) *Inoculation of guinea pigs*. Each of at least five guinea pigs, each weighing 350-450 grams, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 5.0 ml. of the monovalent virus pool to be tested. The animals shall be observed for at least 42 days and daily rectal temperatures recorded for the last three weeks of the test. Each animal that dies after the first 24 hours of the test, or is sacrificed because of illness, shall

be necropsied. The tissue shall be examined both microscopically and culturally for evidence of tubercle bacilli, and by passage of tissue suspensions into at least three other guinea pigs by the intracerebral and intraperitoneal routes of inoculation for evidence of viral infection. If clinical symptoms suggest infection with lymphocytic chorlomeningitis virus, serological tests shall be performed on blood samples of the test guinea pigs to confirm the clinical observations. Animals that die or are sacrificed during the first three weeks after inoculation with poliovirus shall be examined for infection with lymphocytic choriomeningitis virus. Animals that die in the final three weeks shall be examined both microscopically and culturally for M tuberculosis. The monovalent virus pool is satisfactory for poliovirus vaccine only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with M Tuberculosis, or any viral infection.

(5) *Inoculation of monkey kidney tissue cultures.* At least 500 doses or 50 ml., whichever represents a greater volume of virus, of each undiluted monovalent virus pool or in equal proportions from individual harvests or sub-pools, shall be tested for simian viruses in Macaca, and the same volume in Cercopithecus, monkey kidney tissue culture preparations, in a ratio of inoculum to medium of from 1:1 to 1:3, and with the area of surface growth of cells at least three square centimeters per milliliter of test inoculent, after neutralization of the poliovirus by high titer type specific non-simian antisera. The immunizing antigens used for the preparation of antisera shall be grown in a human tissue culture cell line. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for

poliovirus vaccine only if all the tissue cultures fail to show evidence of the presence of simian viruses.

(6) *Inoculation of human cell cultures.* At least 500 does or 50 ml., whichever represents a great volume of virus, taken from either a single monovalent or in equal proportions from individual harvests or sub-pools, shall be tested in a ratio of inoculum to medium of 1:1 to 1:3, and with the area of surface growth of cells at least three square centimeters per milliliter of test inoculum, for the presence of measles/virus in either (i) primary human amnion cells, or (ii) primary human kidney cells, or (iii) any other cell system of comparable susceptibility to unmodified measles virus. The test material shall be neutralized with poliovirus antiserum of non-simian derivation if the tissue culture cell system used is susceptible to poliovirus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of measles virus.

(7) *Inoculation of rabbit kidney tissue cultures.* At least 500 ml. of virus pool taken from either a single monovalent pool or in equal proportions from individual harvests or sub-pools, shall be tested in a ratio of inoculum to medium of from 1:1 to 1:3, and with the area of surface growth of cell at least three square centimeters per milliliter of test inoculum, in primary rabbit kidney tissue culture preparations for evidence of B-virus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of B-virus.

(b) *Tests after filtration.* The following tests relating to safety shall be performed after the filtration process

on each monovalent virus pool or on each multiple thereof (monovalent lot);

(1) *Neurovirulence in monkeys.* Each monovalent virus pool or monovalent lot shall be tested in comparison with the NIH Reference Attenuated Poliovirus for neurovirulence in Macaca monkeys by both the intrathalamic and intraspinal routes of injection. A pre-injection serum sample obtained from each monkey must be shown to contain no neutralizing antibody in a dilution of 1:4 when tested against no more than 1,000 TCID of each of the tree types of poliovirus. The neurovirulence tests are no valid unless the sample contains at least 10 TCID per ml. when titrated in comparison with the NIH Reference Poliovirus, Live, Attenuated of the appropriate type. All monkeys shall be observed for 17 to 21 days, under the supervision of a qualified pathologist, physician or veterinarian, and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(i) *Intrathalamic inoculation.* Each of at least ten Macaca monkeys shall be injected intrathalamically with 1.0 ml. of virus pool material containing at least 10 TCID per ml. and each of at least ten additional Macaca monkeys shall be injected intrathalamically with 1.0ml. of a 10 dilution thereof. Comparative evaluations shall be made with the virus pool under test and the NIH reference material. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily.

(ii) *Intraspinal inoculation.* Each of a group of at least five Macaca monkeys shall be injected intraspinally with 0.2 ml. of virus pool material containing at least 10 TCID per ml. and each monkey in four additional groups of at least five Macaca monkeys shall be injected

intraspinally with 0.2 ml. 10^{-}, 10^{-}, 10^{-}, and 10 dilutions thereof, respectively. Comparative evaluations shall be made with the virus pool under test and the NIH reference material. Only monkeys that show microscopic evidence of inoculation into the gray matter of the lumbar cord shall be considered as having been injected satisfactorily.

(iii) *Determination of neurovirulence.* At the conclusion of the observation period comparative histopathological examinations shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, and mesencaphalon of each monkey in the groups injected with virus under test and those injected with the NIH Reference Attenuated poliovirus, except that for animals dying during the test period these examinations shall be made immediately after death. The animals shall be examined to ascertain whether the distribution and histological nature of the lesions are characteristic of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the NIH Reference Attenuated Poliovirus with respect to (a) the number of animals showing lesions characteristic of poliovirus infection, (b) the number of animals showing lesions other than those characteristic of poliovirus infection, (c) the severity of the lesions, (d) the degree of dissemination of the lesions, and (e) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. The virus pool under test is satisfactory for poliovirus vaccine manufacture only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrate that the neurovirulence of the test virus pool does not exceed that of the NIH Reference Attenuated Poliovirus.

(2) *Test for virus titer.* The concentration of living virus in each monovalent virus pool or lot shall be determined using the NIH Reference Poliovirus Live, Attenuated of the same type as a control. The test shall be a 50 percent end-point titration calculation (TCID), performed with either groups of ten tubes at 1 log dilution steps or groups of five tubes of 0.5 log dilution steps, or a test of demonstrated equivalent sensitivity. Acceptable titrations of the reference virus shall not vary more than 0.5 log from its labeled titer.

(3) *Tests for In-vitro Markers.* A test shall be performed on each monovalent virus pool or each monovalent lot resulting therefrom using the rct/40 Marker and at least one of the other marker methods described below. The test results shall demonstrate that the virus under test and the seed virus have substantially the same marker characteristics.

(i) *rct/40 Marker.* Attenuated strains which grow readily at 40? C. (+0.5? C) are classified as rct/40 positive (+) in contrast to the rct/40 negative (?) strains which show an increased growth of at least 100,000 fold at 36? C over that obtained at 40? C. Comparative determination shall be made in either tube or bottle culture.

(ii) *d Marker.* Attenuated strains which grow readily at low concentrations of bicartionate under agar are classified as d positive (+) strains which exhibit delayed growth under the same conditions. The cultures shall be grown in a 36? C incubator either in stoppered bottles or in plates in an environment of 5 percent CO, in air.

(iii) *MS Markers.* Attenuated strains which grow more readily on monkey stable (MS) cells are classified as MS positive (+) in contrast to MS negative (?) strains. Com-

parative determinations shall be made in either tube cultures or in bottle cultures under agar.

(4) *Test for sterility.* The final bulk vaccine of each monovalent virus pool, or each monovalent lot resulting therefrom, shall be tested for sterility in both fluid Thioglycollate and Sabouraud media by the procedure prescribed in § 73.73 with a sample of no less than 10 ml. for each test.

§ 73.115 Potency test.

The concentration of live virus express ad TCID, of each type in the vaccine shall constitute the measure of its potency. The accuracy of the titration to determine the concentration of live virus in the lot under test shall be confirmed by performing a titration with the NIH Reference Poliovirus, Live, Attenuated of the appropriate type as a check on titration technique. The concentration of each type of live virus contained in the vaccine of the lot under test shall be between 200,000 and 500,000 TCID per human dose.